Tenofovir disoproxil fumarate

Essential medicine status

Section: 6. Anti-infective medicines > 6.4. Antiviral medicines > 6.4.4. Antihepatitis medicines > 6.4.4.1. Medicines for hepatitis B > 6.4.4.1.1. Medicines for hepatitis B > Nucleoside/Nucleotide reverse transcriptase inhibitors

ATC codes: J05AF07

Indication	Chronic hepatitis B ICD11 code: 1E51.0Z
INN	Tenofovir
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid: 300 mg tablet (equivalent to 245 mg tenofovir disoproxil)
EML status history	First added in 2015 (TRS 994)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Tenofovir disoproxil fumarate
DrugBank	Tenofovir disoproxil fumarate (Tenofovir disoproxil)

Summary of evidence and Expert Committee recommendations

An application was submitted by Dr Philippa Easterbrook, WHO Global Hepatitis Programme, Department of HIV/AIDS, for the addition of entecavir to the EML and EMLc for the treatment of chronic hepatitis B infection. In addition, a separate application was submitted by Gilead Sciences Inc., California, USA, for the addition of tenofovir disoproxil fumarate (TDF) to the EML for the treatment of chronic hepatitis B. TDF is currently included in the Model List as an antiretroviral agent. The Committee noted that the requests for inclusion of these medicines reflect recent WHO guidelines (2015) for the treatment of chronic hepatitis B (1). These guidelines recommend treatment with either tenofovir or entecavir. Entecavir is the recommended agent for use in children aged 2–11 years. Tenofovir is licensed for use in those aged 12 years and above. Nucleoside/nucleotide analogues (NAs) with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended in the WHO guidelines (1). It is expected that inclusion of entecavir and tenofovir in the Model List will help facilitate the scale-up of hepatitis B treatment. Expert reviews of the applications were prepared by two members of the Expert committee. Comments in support of the entecavir application were received from Dr Myriam Henkens, International Medical Coordinator, Medecins Sans Frontieres. Correspondence in support of the applications was also received from the WHO Department of HIV/AIDS and Global Hepatitis Programme. Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus that infects the liver, causing hepatocellular necrosis and inflammation. Chronic hepatitis B (CHB) is defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. The disease is a major public health problem; an estimated 240 million people were chronically infected worldwide in 2005, with a disproportionally large burden of HBsAg infection in all sub-Saharan African regions and east Asia (2). Although most carriers will not develop hepatic complications from CHB, 15–40% will develop serious sequelae during their lifetime, including cirrhosis and hepatocellular carcinoma (HCC) (3). Several interventions have the potential to dramatically reduce the burden of HBV infection. By 2011, hepatitis B immunization programmes had been introduced in 180 countries, targeting infants (first dose at birth), and have been highly effective in reducing the incidence and prevalence of hepatitis B in many endemic countries (4). However, the applications emphasized that, despite these advances, viral hepatitis is not being systematically addressed in most countries, and it will be several decades until the immunization programmes have an impact on

HBV-related deaths. At present, CHB cannot be cured in most people, and the goal of treatment is therefore to suppress viral replication which reduces (or reverses) progression of liver fibrosis and cirrhosis, thereby reducing the risk of liver failure, HCC and death. Long-term (potentially lifelong) therapy is required for the majority of patients (1). Since the 1990s, NAs and interferon (IFN)-alpha have been widely used for the treatment of CHB. The NAs currently licensed are lamivudine, telbivudine, adefovir, tenofovir and entecavir. Development of viral resistance as a result of mutations in the viral DNA during replication is the primary limitation of most oral antiviral agents. The National Clinical Guideline Centre in the United Kingdom reports that very low rates of drug resistance are recorded for entecavir compared with adefovir, lamivudine and telbivudine (5). At present, no induced drug resistance mutations caused by tenofovir treatment have been clearly identified. A series of systematic reviews and a network meta-analysis, commissioned as part of the WHO guideline development process, confirm the efficacy of entecavir. In the treatment of naive, hepatitis B e antigen-positive (HBeAgpositive) Asian CHB patients, undetectable HBV DNA levels were achieved in more entecavir-treated patients than in those treated with adefovir (RR 1.73; 95% CI: 1.38–2.17) (6). Compared with lamivudine, entecavir showed greater efficacy in terms of improved liver histology (RR 1.16; 95% CI 1.07–1.26), normalization of serum alanine aminotransferase (ALT) (RR 1.15; 95% CI: 1.11–1.2) and HBV DNA loss (RR 1.65; 95% CI: 1.37 to 1.98) (7). After three and five years of treatment with entecavir there were low cumulative rates of mortality (3% and 3.8%) and HCC (3.9% and 6.6%). The cumulative probability of developing genotypic resistance to entecavir was low at three years (1.2–3.3%) and five years of treatment (0.8–1.2%) (8-12). Similar effectiveness of entecavir compared with lamivudine and lamivudine plus adefovir was apparent in adult treatment-naive patients with decompensated cirrhosis (13, 14). Although data on use in children are more limited, there is evidence of high virological response to tenofovir in adolescents, with normalization of serum ALT at 72 weeks treatment and no observed viral resistance (15) and an ongoing placebo-controlled trial of entecavir in children (AI463189) which showed entecavir to be superior to placebo at reducing HBV DNA to less than 50 IU/mL, HBeAg seroconversion and normalization of serum ALT levels at 48 weeks of treatment (16). Two double-blind, phase III studies compared tenofovir with adefovir in patients with HBeAg-negative or HBeAg-positive CHB (17). The studies concluded that tenofovir had greater antiviral efficacy than adefovir and a similar safety profile. In the trial on patients with HBeAg-positive CHB, treatment with tenofovir resulted in a significantly higher proportion of patients with undetectable serum HBV (76% versus 13%), ALT normalization (68% versus 54%) and HBsAg loss (3% versus 0%). In the trial on patients with HBeAgnegative CHB, 48 weeks of treatment with tenofovir resulted in significantly more patients with undetectable serum HBV-DNA than treatment with adefovir (93% versus 63%). Tenofovir resistance was not detected in any of the patients after up to 96 weeks of treatment; it should be noted, however, that patients at the greatest risk of drug resistance received additional therapy with emtricitabine. Based on the available evidence, a network meta-analysis, including a total of 21 pair-wise comparison randomized controlled trials (RCTs) comprising 5 073 HBeAg-positive nucleoside-naive persons and 16 trials comprising 2 604 HBeAg-negative nucleoside-naive persons, showed that individuals treated with tenofovir monotherapy had the highest probability of achieving undetectable HBV DNA at the end of 1 year of treatment. This result was observed in both HBeAg-positive (94.1%; 95% CI: 74.7–98.9%) and HBeAg-negative (97.6%; 95% CI: 56.7–99.9%) persons (1). For entecavir treatment, the result was 64.5% (95% CI: 49.1–80.5%) in HBeAg-positive and 91.9% (95% CI: 87.3–95.1%) in HBeAg-negative individuals. With regard to safety, both entecavir and tenofovir seem to be well tolerated drugs with minimal side-effects. The National Clinical Guideline Centre does note that further research should be undertaken to determine the long-term safety of tenofovir, including the risk of clinically significant hypophosphataemia and related bone toxicity in people with CHB (5). No significant differences in tolerability and renal parameters are reported between treatment with entecavir and tenofovir (18). It is recommended that baseline renal function be measured and baseline risk for renal dysfunction assessed in all individuals before initiation of antiviral therapy. Renal function should be monitored annually in persons on long-term tenofovir and entecavir therapy and growth should be monitored carefully in children when entecavir is administered. The Committee noted that, compared with lamivudine and other NAs with a low barrier to resistance, entecavir and tenofovir have a high genetic barrier to resistance and very low observed rates of drug resistance over long term follow-up. It was also noted, however, that resistance to entecavir occurs frequently in individuals with lamivudine resistance (1). The Expert Committee noted that, according to the WHO Global Price Reporting Mechanism, the minimum treatment cost per year for tenofovir is US$ 36, with a median of US$ 46. The Committee also noted advice from the applicant of their pricing strategies and licensing agreements in low- and middle-income countries. Although studies presented in the application showed entecavir to be either cost–effective or the preferred strategy (19-23), the Committee noted that the production cost of entecavir has been estimated to be far below the price currently charged (24). Taking into consideration the significant public health need, the clear evidence from RCTs supporting the role of both medicines in various CHB treatment regimens , and the inclusion of these medicines in the recently released WHO guidelines for the prevention, care and treatment of chronic hepatitis B infection, the Expert Committee therefore recommended

the addition of tenofovir and entecavir to the core list of the EML and the addition of entecavir to the core list of the EMLc for the treatment of chronic hepatitis B under a new section (Antihepatitis medicines) and subsection (Medicines for hepatitis B).

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